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# Metal-Free $\alpha$-Amination of Secondary Amines: Computational and Experimental Evidence for Azaquinone Methide and Azomethine Ylide Intermediates

Arne Dieckmann,[†] Matthew T. Richers,[‡] Alena Yu. Platonova,[‡,§] Chen Zhang,[‡] Daniel Seidel,[‡,*] and K. N. Houk*[,†]

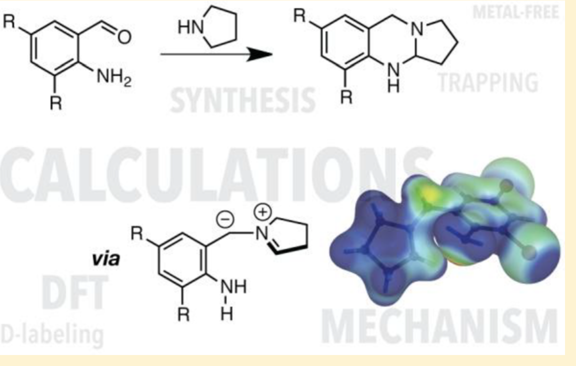
[†]Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States

[‡]Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08854, United States

[§]Department of Organic Synthesis Technology, Ural Federal University, Yekaterinburg, 620002, Russia

Supporting Information

**ABSTRACT:** We have performed a combined computational and experimental study to elucidate the mechanism of a metal-free $\alpha$-amination of secondary amines. Calculations predicted azaquinone methides and azomethine ylides as the reactive intermediates and showed that iminium ions are unlikely to participate in these transformations. These results were confirmed by experimental deuterium-labeling studies and the successful trapping of the postulated azomethine ylide and azaquinone methide intermediates. In addition, computed barrier heights for the rate-limiting step correlate qualitatively with experimental findings.




## INTRODUCTION

Aminal substructures[1] are present in a number of natural products,[2] which makes simple synthetic procedures to their precursors and analogues important to the organic chemist. Recently, one of our groups developed an efficient route to ring-fused aminals[3,4] by metal-free, redox-neutral[5] C−H functionalization of cyclic amines (Scheme 1).[6,7] The procedure is straightforward and only requires heating an aminobenzaldehyde with an excess of amine in ethanol to afford the aminal in one step. Most methods that involve the functionalization of relatively nonreactive C−H bonds require the use of transition-metal catalysts, often in combination with (super)stoichiometric amounts of oxidant.[8] Here, we report the results of a computational and experimental study aimed at delineating the mechanistic pathways of this practical and convenient transformation. The mechanism was predicted by an extensive exploration of possible pathways using density functional theory (DFT) calculations based on the original experimental results[3,4] and is in line with subsequently performed deuterium-labeling and trapping experiments.

Some of the key findings of the initial investigation are summarized in eqs 1−4. The scope of the aminal formation includes different cyclic secondary amines and electron-deficient *o*-aminobenzaldehydes were found to work best. Interestingly, not only the electronic structure, but also the geometry of the amines, has a profound effect on reactivities and yields. Pyrrolidine gives excellent yields with electron-poor aminobenzaldehydes such as **1a** (eq 1). Good yields can also be obtained with more electron-rich aminobenzaldehydes (e.g., **1b**), although extended reaction times are required. Even with the highly reactive aminobenzaldehyde **1a**, piperidine requires prolonged reaction times at elevated temperatures and the yield drops significantly (eq 2). Morpholine is even less reactive. Cyclic amines with benzylic $\alpha$-C−H bonds such as 1,2,3,4-tetrahydroisoquinoline (THIQ) are excellent substrates (eq 3). In contrast, no product could be obtained with 1,2,3,4-tetrahydroquinoline (THQ) under a variety of conditions (eq 4).

Various potential mechanisms have been considered for these transformations, all of which are in line with experimental conditions. Using the reaction of **1b** and pyrrolidine as a prototypical example, a number of potential mechanistic pathways are summarized in Scheme 1. All start with the formation of hemiaminal **3b** that should be formed rapidly upon mixing of the aldehyde and amine. Afterward, **3b** can eliminate hydroxide to form iminium ion **4b**, which can undergo a variety of reactions. Deprotonation by an external base either leads to *o*-aza-quinone methide **5b**[9] or azomethine ylide **6b**.[10,11] Aza-quinone methide **5b** can also be obtained by a direct dehydration of hemiaminal **3b** (vide infra). Alternatively, the protonated azomethine ylide **10b** can be formed by an internal proton transfer[12] and is likely to undergo another

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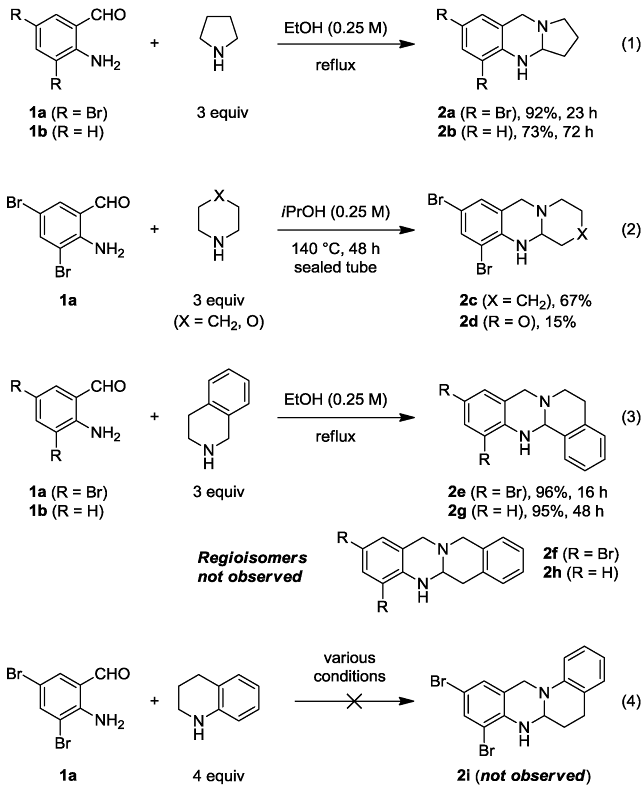



proton transfer resulting in iminium species **8b**. In addition to the rather unlikely pathway involving **10b** as an intermediate, iminium ion **8b** can be obtained from **5b** via azomethine ylide **6b**. The latter could be formed from **5b** either by a 1,6-hydride shift[13] or a 1,6-proton transfer.[12] Subsequent protonation of azomethine ylide **6b**, e.g., by solvent molecules, results in **8b**. The ring closure can either proceed via iminium ion **8b** or zwitterion **7b**. An intramolecular attack of the amino group nitrogen on the iminium moiety in **8b** leads to the protonated product **9b**, while the formation of **7b** by a (solvent-mediated) proton transfer and a subsequent intramolecular attack leads to the neutral product **2b**. The direct transformation of **4b** to **8b** via 1,3-hydride shift was not considered.[14]

Overall, there are several plausible and interconnected mechanisms leading to products **2** that differ with respect to the intermediates involved and their protonation states. As a consequence, a purely experimental mechanistic elucidation of this reaction is likely to be extremely challenging. In order to discriminate between the different mechanistic possibilities, we undertook a detailed computational study based on DFT and arrived at a consistent, but partly unexpected mechanism. In addition, new experimental data were obtained on selectivities and reactivities of different substrates, and deuterium-labeling studies were performed that provide evidence that supports the computational results. Further support was obtained by trapping of an azomethine ylide and an azaquinone methide.

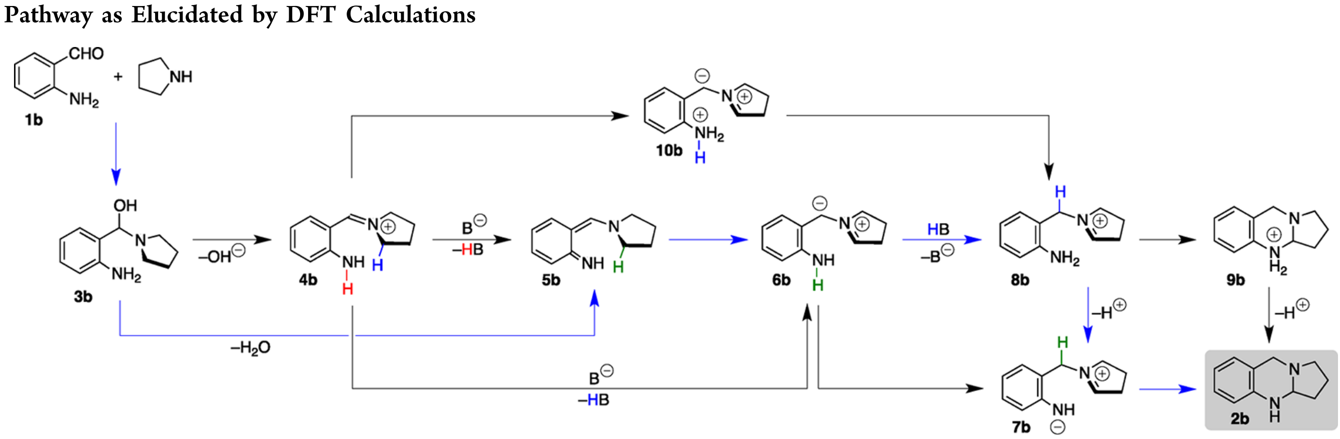
For the sake of clarity, we will first provide our new experimental results. Afterward, we will discuss our calculations and rationalize the experimental findings based on the predicted mechanism.

## ■ EXPERIMENTAL RESULTS AND DISCUSSION

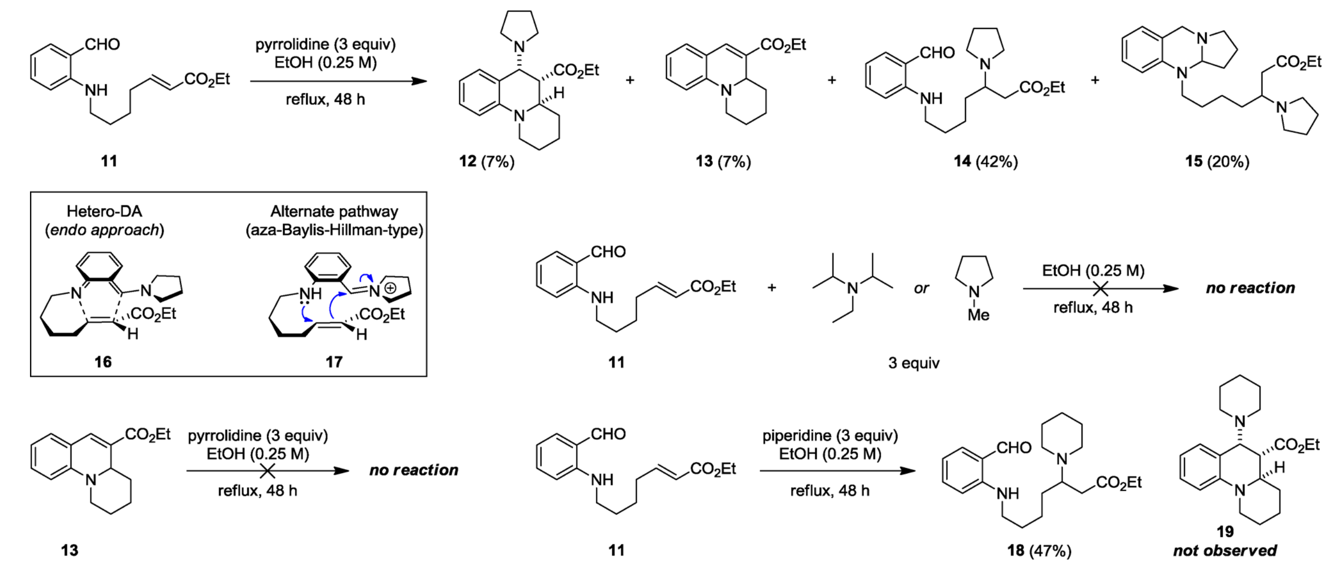
**Evidence for the Intermediacy of Azaquinone Methides.** In order to support or rule out the mechanistic pathways presented in Scheme 1, we designed a number of experiments with the goal to trap some of the proposed intermediates, in particular *o*-azaquinone methides (e.g., **5b**) and azomethine ylides (e.g., **6b**). After a series of failed attempts to trap the proposed quinoidal intermediates via intermolecular hetero-Diels–Alder reactions, we explored the possibility of tethering a dienophile to one of the reactants. To this end, we prepared aminobenzaldehyde **11** bearing an $\alpha,\beta$-unsaturated ester attached to nitrogen via a four-carbon alkyl chain linker (Scheme 2). Upon exposure of **11** to standard aminal forming conditions with excess pyrrolidine, we recovered compound **12** in 7% yield, the apparent product of an endoselective hetero-Diels–Alder reaction (see structure **17**). Another product that was isolated from the reaction mixture is compound **13** (7%), possibly formed upon elimination of pyrrolidine from compound **12**. In addition, we obtained conjugate addition product **14** (42%), aminal **15** (20%),[15] and recovered starting material **11** (9%). While these results are consistent with an *o*-azaquinone methide intermediate, we needed to rule out alternative reaction pathways for the formation of **12** that do not involve a [4 + 2] cycloaddition.

Potentially, tricycle **13** could be formed directly in a Baylis–Hillman-like reaction,[16] and a conjugate addition of pyrrolidine to **13** could result in the formation of apparent Diels–Alder product **12**. We tested for this possibility in a series of experiments (Scheme 2). Heating **11** in the absence of any additives did not lead to formation of **13**. Since pyrrolidine could simply act as a base to catalyze cyclization of tethered alkene **11** to yield cyclization product product **13**, we also performed the reaction in the presence of Hünig's base (similar $pK_{aH}$ to pyrrolidine) and *N*-methylpyrrolidine. No reaction was observed in either case, and starting material **11**

**Scheme 1. Potential Mechanistic Pathways for the Redox-Neutral Aminal Formation. Blue Arrows Refer to the Lowest Energy Pathway as Elucidated by DFT Calculations**



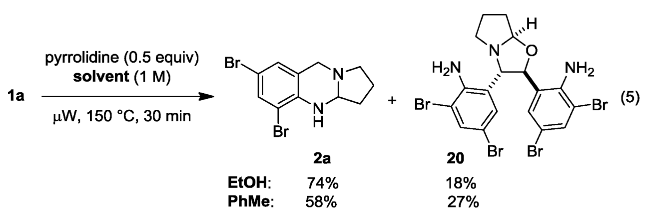
**Scheme 2. Capture of an *o*-Azaquinone Methide Intermediate via Intramolecular [4 + 2] Cycloaddition and Relevant Control Experiments**




was recovered quantitatively. Furthermore, to ensure that the apparent Diels–Alder product **12** is not the product of conjugate addition of pyrrolidine to tricycle **13**, the latter was exposed to pyrrolidine in refluxing ethanol for 48 h. No reaction was observed in this instance. This strongly suggests that **12** is not a conjugate addition product, but rather that **13** results from the elimination of pyrrolidine from **12**.

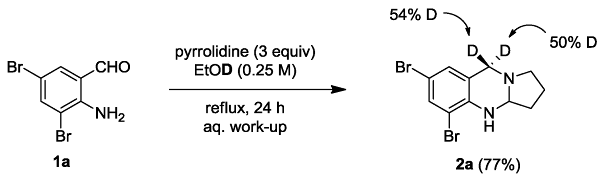
An aza-Baylis–Hillman-type pathway[16] (e.g., structure **17** in Scheme 2) would also account for the formation of **12**. However, given the unlikeliness of iminium ion formation under the reaction conditions (see the Computational Results), this pathway was not considered further. Interestingly, the analogous reaction of **11** with piperidine only led to conjugate addition product **18** in 47% yield, in addition to recovered starting material. The lack of formation of **19** or the corresponding aminal product can be attributed to an increased difficulty of accessing the required *ortho*-azaquinone methide or azomethine ylide intermediates. Another possible pathway, namely pyrrolidine acting as a nucleophilic Lewis base catalyst in an intramolecular Baylis–Hillman reaction was ruled out on the basis that this would require the formation of an intermediate with a 10-membered ring (not shown).

**Evidence for the Intermediacy of Azomethine Ylides.** Aldehydes are known to act as potent dipolarophiles in reactions with azomethine ylides.[17] In cases where azomethine ylides are formed from amino acids and aldehydes in the presence of other dipolarophiles, these cycloadditions can become unintended side reactions. We decided to exploit this reactivity pattern to establish the intermediacy of azomethine ylides in the aminal formation. In order to promote intermolecular [3 + 2] cycloaddition and hopefully suppress aminal formation, pyrrolidine was allowed to react with 2 equiv of aminobenzaldehyde **1a** (eq 5). The reaction was performed in ethanol solution 4-fold more concentrated than under




standard conditions. A microwave reactor was used to facilitate product formation. Following a reaction time of 30 min at 150 °C, cycloaddition product **20** was isolated in 18% yield along with aminal **2a** (74%). When toluene was used as the solvent under otherwise identical conditions, the yield of the [3 + 2] product **20** increased to 27%, while aminal **2a** was recovered in 58% yield. This increase in yield in an apolar solvent is consistent with a reduced quantity of proton sources available to protonate the azomethine ylide. In both solvents, **20** was obtained as a single diastereomer. The relative stereochemistry of **20** matches that of the major products previously reported in analogous [3 + 2] reactions.[17] These observations strongly support the intermediacy of an azomethine ylide.

**Deuterium-Labeling Studies.** A number of deuterium-labeling experiments were performed in order to obtain further insights into the mechanism of the aminal formation. When a reaction of aminobenzaldehyde **1a** and pyrrolidine was conducted in EtOD, aminal **2a** was obtained with close to 100% incorporation of one deuterium atom, distributed approximately equally over the two diastereotopic benzylic protons (eq 6).[18] To confirm that deuteration occurred during aminal formation, nondeuterated **2a** was exposed to identical reaction conditions (reflux in EtOD for 48 h in the presence of 2 equiv of pyrrolidine). No trace of deuterium incorporation was observed in this case. These results are consistent with an azomethine ylide intermediate related to **6b** being protonated by solvent to form an iminium ion of type **8b**. The corresponding experiment was also performed with THIQ (eq 7). Interestingly, in this case partial deuterium incorporation was observed for all three benzylic protons with a total deuterium incorporation of ~100%. The observation of deuterium incorporation at the aminal carbon likely reflects a difference in charge distributions of the azomethine ylides derived from pyrrolidine vs THIQ.[19] However, the fact that substantially less than one deuterium atom was incorporated into the two diastereotopic benzylic positions of the dibromoaniline ring seemed at odds with the proposed mechanism. One possible explanation would be that the protonation step exhibits a relatively large kinetic isotope effect. The two starting materials could serve as a source of protons. In order to minimize the total number of protons available in the system, we repeated this experiment with substrates in which the exchangeable protons had been replaced with deuterium (eq 8). Indeed, in the event,



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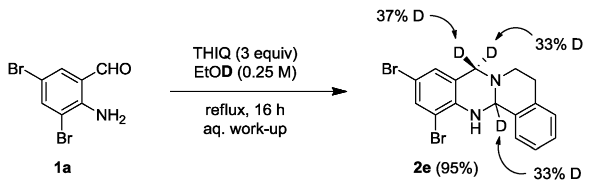

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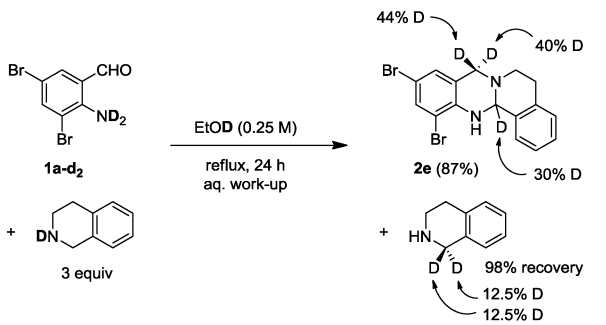
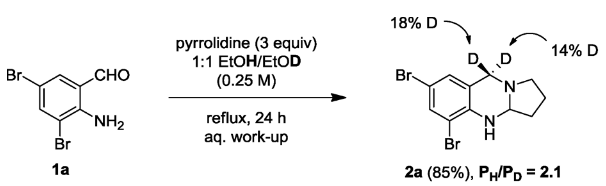


(8)

substantially increased deuterium incorporation was observed in the benzylic position of the dibromoaniline ring. Interestingly, the recovered THIQ was found to be partially deuterated, indicating the reversibility of the early reaction steps. Deuteration of the benzylic position of THIQ requires the presence of **1a** (i.e., heating of THIQ in EtOD under reflux for 16 h did not lead to any incorporation of deuterium into the benzylic position of THIQ).

Deuterium labeling experiments were also used to potentially gain some insights into the nature of the rate-limiting step of the reaction by measuring the kinetic isotope effect (KIE). As the relatively long reaction times and high temperatures required for aminal formation would make spectroscopic monitoring of the progress rather difficult, we chose to measure isotope effects with $P_H/P_D$ values from competition experiments rather than determining $K_H/K_D$ from reaction rates.[20] A reaction of aminobenzaldehyde **1a** and pyrrolidine was conducted in a 1:1 mixture of EtOH and EtOD (eq 9). A $P_H/P_D$ value of 2.1 was observed, which would be



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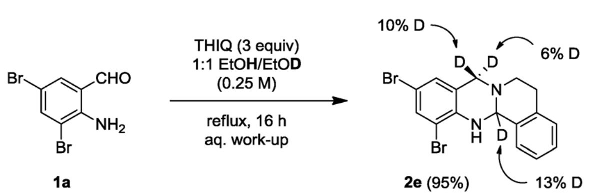
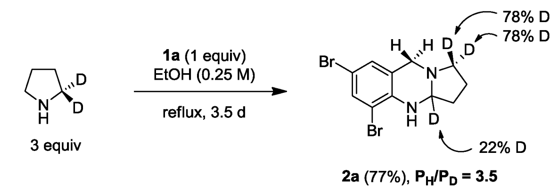


(10)

consistent with the protonation step being rate determining. A similar outcome was observed in the corresponding experiment with THIQ (eq 10). However, calculation of a meaningful $P_H/P_D$ value is complicated by the above-mentioned complexities (see eqs 7 and 8). Regardless, there appears to be a substantial KIE.[21]

The relative rates of C−H vs C−D functionalization were probed with partially deuterated amine substrates (eqs 11−13). A reaction



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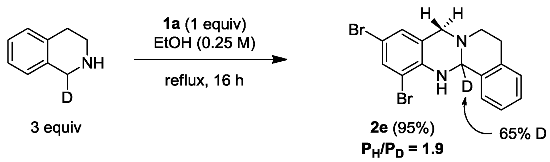

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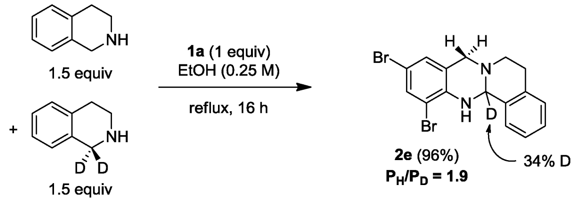

(13)

of pyrrolidine-*2,2-d*$_2$ with **1a** resulted in the formation of partially deuterated **2a** in 77% yield (eq 11). The observed $P_H/P_D$ value of 3.5 is consistent with the C−H functionalization step being rate determining. A substantially lower $P_H/P_D$ value of 1.9 was observed in the corresponding reaction with THIQ-*1-d* (eq 12). A related competition experiment with a 1:1 mixture of THIQ and THIQ-*1,1-d*$_2$ also gave rise to a $P_H/P_D$ value of 1.9 (eq 13). The experiments in eqs 11−13 conclusively rule out the intervention of a 1,3-hydride shift, as no measurable amount of deuterium was incorporated into the benzylic position of the dibromoaniline ring. Overall, the isotopic labeling experiments outlined in eqs 6−13 do not rule out azomethine ylide protonation or C−H functionalization as the rate limiting step.

**Regioselectivity of the Aminal Formation for Nonsymmetrical Amines.** Insights into the mechanism of the aminal formation may also be obtained from nonsymmetrical amines that could, at least in principle, give rise to different regioisomeric products. As shown previously, the reaction of THIQ and aminobenzaldehyde **1b** under standard conditions gave rise to product **2g** in high yield, resulting from exclusive functionalization of a benzylic C−H bond (eq 3). This outcome is entirely anticipated on the basis of the generally observed greater reactivity of benzylic over aliphatic C−H bonds. We were thus surprised to observe trace amounts of regioisomeric product **2h** when this reaction was first conducted under microwave conditions with the initial goal of simply enhancing the reaction rate. Closer inspection revealed that substantial amounts of product **2h** can be obtained at higher temperatures (eq 14). Specifically, a reaction of **1b** and THIQ, conducted under microwave irradiation at 250 °C for 30 min, gave rise to **2h** in 16% yield in addition to the expected product **2g** which was isolated in 72% yield. Moreover, extending the reaction time from 30 min to 2 h led to the formation of **2h** as the major product in 47% yield, without significantly affecting the combined yield of **2g** and **2h**. These observations suggest that aminal **2g** is in fact the kinetic product of this transformation whereas **2h** represents the thermodynamically more stable aminal product. Furthermore, there appears to be a pathway for product isomerization. Prompted by this discovery, we decided to investigate the reaction of


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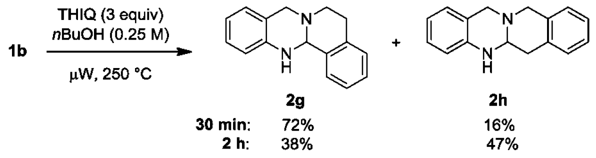

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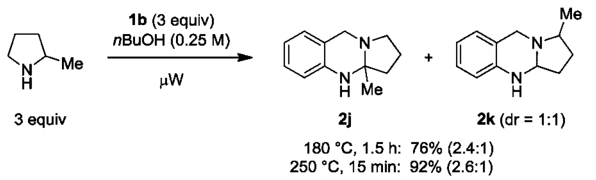


(15)

2-methylpyrrolidine with aminobenzaldehyde **1b** (eq 15). Interestingly, for this particular substrate combination, virtually identical product ratios were obtained under a variety of conditions. Aminal **2j** was consistently obtained as the major product, illustrating the preferential functionalization of a tertiary over a secondary C−H bond. These results are consistent with our previous findings in a reaction of 2-methylpyrrolidine with **1a** which was conducted under reflux.[3a]

## ■ COMPUTATIONAL METHODS

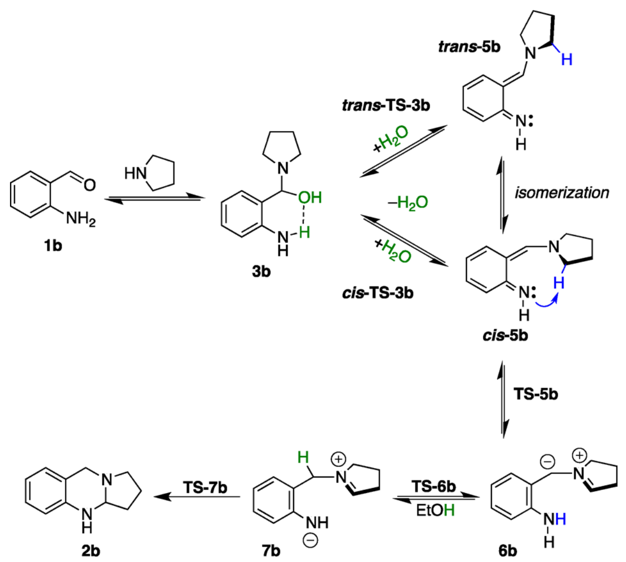
Geometry optimizations were performed with the meta-hybrid density functional M06-2X[22] and a 6-31+G(d,p) basis set. Solvation by ethanol was taken into account by the SMD solvent model,[23] which was applied to both optimizations as well as frequency calculations. It was recently shown that the presence of a polarizable continuum model does not have a great impact on frequencies, while it might be mandatory to locate certain transition states that only exist in polar media.[24] Thermal corrections were calculated from unscaled harmonic vibrational frequencies at the same level of theory for a standard state of 1 mol $L^{-1}$ (17.12 mol $L^{-1}$ for ethanol) and 298.15 K, as the experimental conditions of refluxing ethanol and high pressure in sealed tubes cannot be reproduced. The resulting free energies refer to Gibbs free energies. Free energies as well as enthalpies are corrected for zero-point vibrational energy. All stationary points were characterized and confirmed by vibrational analysis. An ultrafine grid corresponding to 99 radial shells and 590 angular points was used throughout this study for numerical integration of the density. Natural population analyses[25] used the NBO program (version 3.1) as implemented in Gaussian 09. All calculations were performed with Gaussian 09.[26]

## ■ COMPUTATIONAL RESULTS AND DISCUSSION

**General Mechanism.** At the outset of our computational study we considered all mechanisms depicted in Scheme 1. In the following, the mechanism that was predicted to be the most favorable is discussed with the prototypic reaction of amino aldehyde **1b** and pyrrolidine (Scheme 3). A matching free energy profile is shown in Figure 2.

The first step in the reaction cascade is the formation of hemiaminal **3b**, which is exothermic but endergonic according to our calculations. To obtain an iminium ion as suggested in Scheme 1, hydroxide needs to be eliminated. Upon elimination, hydroxide spontaneously abstracts the amine hydrogen leading to a set of two quinoidal intermediates, ***cis*-5b** and ***trans*-5b** (Figure 1). We could also locate transition states ***trans*-TS-3b** and ***cis*-TS-3b**, directly connecting hemiaminal **3b** with ***trans*-5b** and ***cis*-5b** by a concerted elimination of water (Scheme 3 and Figure 2). Both transition states are lower in terms of enthalpy and free energy than the corresponding iminium ion, suggesting that ***trans*-5b** and ***cis*-5b** are formed directly from **3b**

**Scheme 3. General Mechanism for the α-Amination of Nitrogen Heterocycles Is Exemplified with the Prototypic Reaction of 1b and Pyrrolidine Leading to Product 2b**



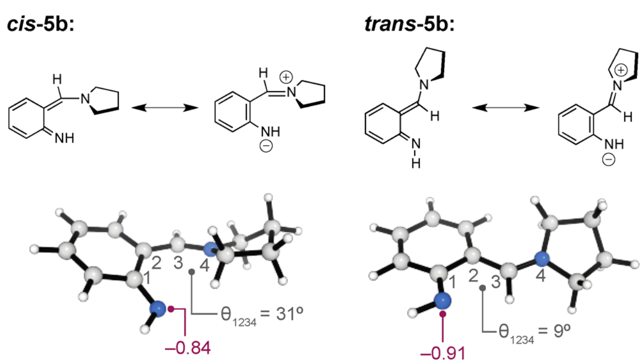


**Figure 1.** Structures of quinoidal intermediates *cis*-**5b** and *trans*-**5b**. Charges for nitrogen atoms were obtained from a natural population analysis. The dihedral angle $\theta$ is a measure for the planarity of the exocyclic $\pi$-system (0° corresponds to a perfectly flat geometry).

and not via iminium species **4b** as assumed before (Scheme 2). As a consequence, pathways involving the iminium ion do not warrant further consideration.

It must be noted that computed enthalpies and as a consequence free energies are overestimated particularly for **TS-3b,** as this transition state benefits greatly from hydrogen bonding of solvent molecules to the leaving water molecule. As a consequence, we consider **TS-3b** (24.7 kcal $mol^{-1}$) to be always lower in enthalpy and free energy than **TS-5b** (15.9/16.9 kcal $mol^{-1}$), which is in perfect agreement with experimental data.

***trans*-TS-3b** and ***cis*-TS-3b** differ with respect to the geometry of substituents at one exocyclic double bond. While ***cis*-5b** allows an abstraction of the α-hydrogens of the heterocycle by the imine nitrogen via **TS-5b,** an intramolecular reaction is impossible in ***trans*-5b**. ***trans*-TS-3b** and ***trans*-5b** are 1 kcal $mol^{-1}$ lower in energy than their corresponding *cis*-isomers due a greater planarity of the resulting exocyclic $\pi$-system (Figure 1), corresponding to a reduced $A^{1,3}$-strain interaction.

A highly negative charge on the primary nitrogen obtained from a natural population analysis in **5b** indicates a significant

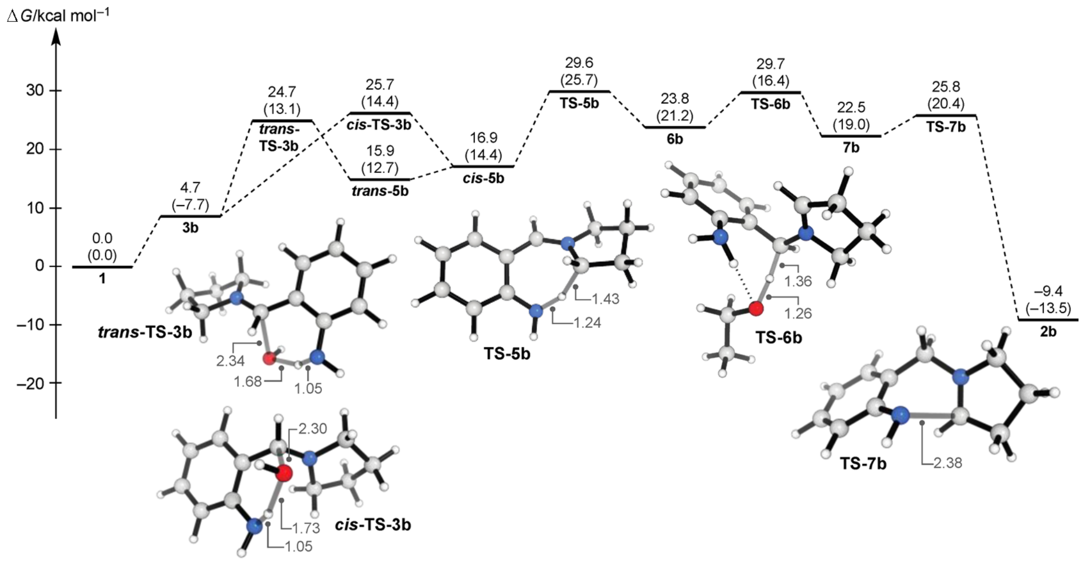



**Figure 2.** Gibbs free energy profile for the reaction depicted in Scheme 3. Free energies and enthalpies in parentheses are given in kcal mol$^{-1}$ and bond lengths in Å.

**Table 1. Free Energies (And Enthalpies in Parentheses) (kcal mol$^{-1}$) for All Intermediates and Transition States (M06-2X/6-31+G(d,p)/SMD(Ethanol))**

| product 2*x* | 3x | *trans*-TS-3x | *cis*-TS-3x | *trans*-5x | *cis*-5x | TS-5x | 6x | TS-6x | 7x | TS-7x | 2x |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **a** | 3.4 (−9.1) | 21.9 (10.3) | 22.6 (11.0) | 11.1 (8.8) | 11.8 (9.8) | 25.1 (21.5) | 18.1 (15.8) | 23.9 (13.6) | 12.9 (11.9) | 17.7 (14.2) | −8.6 (−17.0) |
| **b** | 4.7 (−7.7) | 24.7 (13.1) | 25.7 (14.4) | 15.9 (12.7) | 16.9 (14.4) | 29.6 (25.7) | 23.8 (21.2) | 28.0 (16.4) | 22.5 (19.0) | 25.8 (20.4) | −9.4 (−13.5) |
| **c** | 2.9 (−8.4) | 29.2 (18.2) | 29.2 (18.8) | 13.3 (11.3) | 15.2 (11.3) | 32.1 (29.9) | 23.5 (23.5) | 26.8 (17.9) | 15.9 (14.9) | 17.2 (14.3) | −7.8 (−11.4) |
| **d** | 2.9 (−8.0) | 31.4 (20.0) | 30.8 (20.4) | 16.2 (14.1) | 16.8 (15.5) | 32.9 (30.5) | 26.0 (24.6) | 32.1 (22.0) | 21.4 (19.9) | 21.9 (19.0) | −4.6 (−7.8) |
| **e** | 0.0 (−11.4) | 25.3 (16.2) | 25.5 (16.6) | 15.1 (13.8) | 16.3 (15.0) | 23.1 (20.1) | 14.4 (12.7) | 28.5 (14.8) | 14.0 (13.6) | 15.7 (12.3) | −11.0 (−15.9) |
| **f** | 2.4 (−10.7) | 25.5 (16.5) | 24.2 (16.7) | 16.2 (14.1) | 17.4 (15.3) | 29.8 (26.2) | 23.3 (21.3) | 32.2 (18.0) | 16.4 (16.0) | 19.7 (16.0) | −13.8 (−17.9) |
| **g** | 4.7 (−7.3) | 30.6 (19.2) | 31.5 (20.2) | 20.3 (18.7) | 21.2 (19.6) | 27.5 (24.1) | 19.0 (16.9) | 29.1 (19.1) | 22.7 (20.7) | 24.1 (20.4) | −6.9 (−11.0) |
| **h** | 4.7 (−7.3) | 30.6 (19.4) | 31.4 (20.2) | 20.7 (19.2) | 22.3 (20.0) | 33.9 (30.5) | 28.9 (26.9) | 32.8 (23.2) | 25.7 (24.0) | 27.6 (24.2) | −9.2 (−13.4) |
| **i** | 4.6 (−6.7) | 32.2 (21.4) | 34.1 (22.6) | 20.1 (17.1) | 21.1 (17.9) | 35.6 (31.2) | 32.5 (29.4) | 37.5 (25.3) | 25.4 (22.7) | 27.4 (22.8) | −9.3 (−13.8) |

contribution from a zwitterionic resonance-structure involving an iminium ion at the heterocycle, which restores the aromaticity of the system. Although the *trans*-geometry is slightly preferred, the *cis*/*trans* energy difference is quite small and dihedral scans proved the barrier for isomerization to be lower than the barrier for intramolecular proton transfer (**TS-5b**), so that ***trans*-5b** can be directly converted to ***cis*-5b.** Furthermore, up to this point, all steps are reversible so that ***trans*-5b** may be recycled to ***cis*-5b.** The transition state for an intramolecular proton transfer **TS-5b** has a free energy barrier of 12.7 kcal mol$^{-1}$ relative to ***cis*-5b** and is likely to be the rate-determining step. While a 1,6-hydride shift has been considered before, the substantial negative charge on the nitrogen in **5b** precludes this mechanistic alternative. The intrinsic reaction coordinate associated with **TS-5b** leads to azomethine ylide **6b** (Scheme 3). A natural population analysis of **6b** shows the negative charge resides mainly on the exocyclic methine carbon, which is rapidly protonated by ethanol (**TS-6b**). Experimental deuterium labeling studies with EtOD show deuterium incorporation at this position, supporting our proposed mechanism (vide supra). While the enthalpic barrier of **TS-6b** is negative, the free energy barrier calculated for an ethanol concentration of 17.12 mol L$^{-1}$ has a value of 5.9 kcal mol$^{-1}$ with respect to **6b.** Although we attempted to correct the free energy for the large excess of solvent molecules, it is still substantially overestimated as the entropic penalty for this step can be assumed to be negligible.

The protonation of **6b** is directly followed by deprotonation of the primary amino group by the coordinated ethoxide, which proceeds without a barrier as the resulting zwitterion **7b** is resonance-stabilized. Finally, ring-fused aminal **2b** is formed from **7b** by intramolecular nucleophilic attack on the iminium ion. The free energy barrier for this step is very small (3.3 kcal mol$^{-1}$), resulting in a very short lifetime of **7b.** Product formation is substantially exergonic (−9.4 kcal mol$^{-1}$) and probably irreversible under the experimental conditions.

**Reactions Involving Pyrrolidine, Piperidine, and Morpholine.** Inspection of the reactions of pyrrolidine with aldehydes **1a** and **1b** (Scheme 1) reveals dibromo substitution of the aldehyde to give better yields after shorter reaction times. A comparison of the calculated free energies profiles for both reactions (Table 1) shows the reaction of **1a** and pyrrolidine to proceed via lower lying intermediates and transition states. The phenyl ring of aldehyde **1a** is electron-deficient and induces a better charge delocalization into the aromatic system in all intermediates and transition states following **3a**. This effect is most pronounced in **7a**, which is stabilized by 9.6 kcal mol$^{-1}$ relative to **7b**. The formation of hemiaminal **3a** is also more favorable by 1.3 kcal mol$^{-1}$ than the formation of **3b** owing to the more electrophilic character of the carbonyl group in **1a**. The free energy difference between the rate-determining transition states **TS-5a** and **TS-5b** is 4.5 kcal mol$^{-1}$, which is exclusively caused by the change in electronic structure and explains the higher yield of the reaction involving aldehyde **2a**. Piperidine requires higher reaction temperatures and gives slightly lower yields than pyrrolidine while morpholine gives low yields even at elevated temperatures (eq 2).

The formation of quinoidal intermediates **5c** and **5d** is disfavored in comparison to **5a**. Compounds **5c** and **5d** also partly restore the aromaticity of the aryl-ring by adopting a zwitterionic resonance structure, which involves an exocyclic double bond at the iminium ion. The formation of the latter is less favorable in six-membered than in five-membered rings (see the Supporting Information for calculations on model systems). Free energies of **TS-5c** and **TS-5d** are higher than that of **TS-5a** because **5c** and **5d** require more distortion to adopt the transition-state geometries (Figure 3). This does

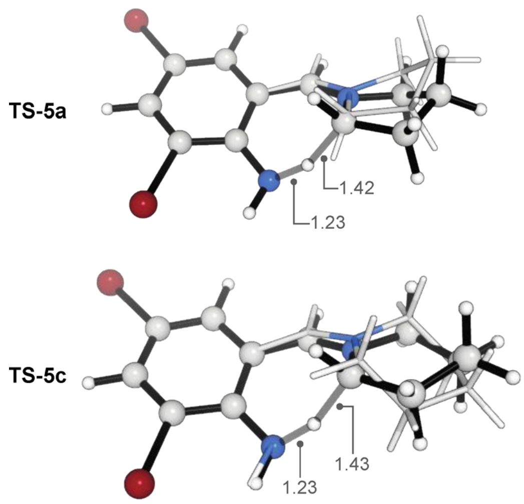



**Figure 3.** Overlay of the geometries of *cis*-**5a** and *cis*-**5c** (sticks) with transition states **TS-5a** and **TS-5c** (balls and sticks).

explain the better experimental performance of pyrrolidine; however no significant discrimination can be made between piperidine and morpholine based on the energies of the rate-limiting steps **TS-5c** and **TS-5d**.

**Reactions Involving THIQ and THQ.** Our experimental results indicate that products **2e** and **2g** are obtained under kinetic control, while **2f** and **2h** represent the thermodynamically stable products. Transition-state energies for **TS-5e** and **TS-5g** are lower by 6.4 and 6.7 kcal mol$^{-1}$ than those of **TS-5f** and **TS-5h**, respectively, confirming the experimental results. This stabilization is caused by the location of the proton to be abstracted in THIQ, which allows an effective delocalization of the resulting charge into the aromatic ring in **6e** and **6g** (Figure 4). However, products **2e** and **2g** are less stable than **2f** and **2h**, respectively, which explains their isomerization at prolonged reaction times. Furthermore, **2g** is predicted to be less stable by 4.1 kcal mol$^{-1}$ than **2e** and thus allows a more facile isomerization.

No product could be obtained at all when THQ was used as an amine instead of THIQ. The high barrier of **TS-5i** is in good agreement with this finding and is partly caused by a substantial distortion required to transform ***cis*-5i** to **TS-5i**. In addition, the reactions to obtain intermediate ***cis*-5i** have a strongly positive reaction free energy (21.1 kcal mol$^{-1}$) as iminium-like structures involving THQ are energetically disfavored (see the Supporting Information), probably due to the conjugation of the nitrogen lone pair with the aromatic ring.

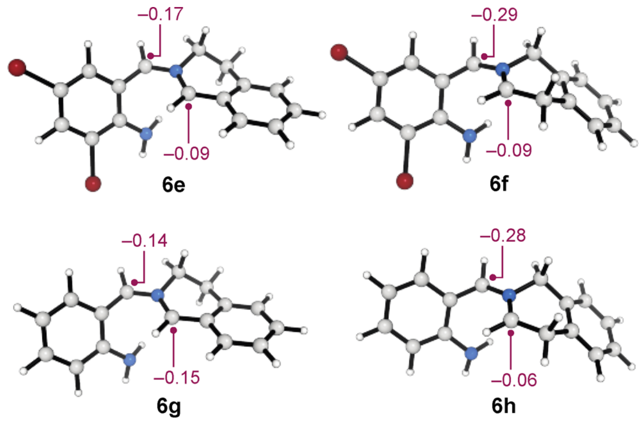



**Figure 4.** Structures and carbon charges of THIQ azomethine ylides.

**Trapping of 6a by a 1,3-Dipolar Cycloaddition.** The azo-methine ylide **6a** could be trapped experimentally by a 1,3-dipolar cycloaddition with aldehyde **1a**. Not surprisingly, the cycloaddition of these highly polar reactants involves a stepwise mechanism with a zwitterionic intermediate **21** (Figure 5).

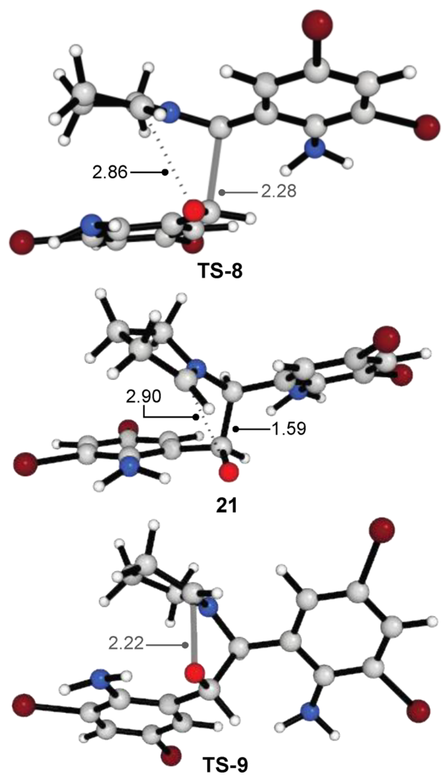



**Figure 5.** Transition states **TS-8** and **TS-9** and zwitterionic intermediate **21** for the [3 + 2] cycloaddition between **1a** and **6a** (see eq 5). The total reaction is exergonic by −35.6 kcal mol$^{-1}$ relative to **1a** and **6a**.

Transition-state **TS-8** for the first bond formation features a distance of 2.28 Å between the reaction centers while the oxygen and iminium carbon are well separated (2.86 Å). The calculated barrier of 1.6 kcal mol$^{-1}$ is significantly lower than any barrier for the amination reaction cascade and indicates that this reaction is essentially diffusion-controlled. However, the rate is limited by the low concentration of azomethine ylide **6a**, which is readily protonated by ethanol being present in huge excess. The formation of the zwitterionic intermediate **21** is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exergonic by −8.1 kcal mol$^{-1}$ and followed by a fast intramolecular ring closure via **TS-9**. The total cycloaddition reaction is exergonic by −35.6 kcal mol$^{-1}$.

## ■ CONCLUSIONS

We have derived a mechanism for the $\alpha$-amination of nitrogen heterocycles by density functional theory calculations involving an unanticipated direct transition of hemiaminals **3** to quinoidal intermediates **5**. Our computations are supported by experimental studies including deuterium labeling and trapping of the predicted azaquinone methide and azomethine ylide intermediates. According to our calculations, the rate-limiting step of the entire reaction cascade is an intramolecular proton transfer **TS-5**; the barrier of this step correlates qualitatively with experimental results. Experimental work toward extending the scope of this reaction in combination with computational predictions is in progress and will be reported in due course.

## ■ EXPERIMENTAL SECTION

**General Information.** Microwave reactions were carried out in a CEM Discover reactor using sealed 10 mL reaction vessels, and temperatures were measured with an infrared temperature sensor. Silicon carbide (SiC) passive heating elements were purchased from Anton Paar. Purification of reaction products was carried out by flash column chromatography using Sorbent Technologies Standard grade silica gel (60 Å, 230−400 mesh). Analytical thin-layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 $F_{254}$ plates. Visualization was accomplished with UV light, potassium permanganate, and Dragendorff−Munier stains followed by heating. Proton nuclear magnetic resonance spectra ($^1$H NMR) are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 7.26 ppm, $(CD_3)_2CO$ at 2.04 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex, br = broad; and coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra ($^{13}$C NMR) are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 77.0 ppm).

**Aminal 2a.** A 10 mL round-bottom flask was charged with 2-amino-3,5-dibromobenzaldehyde (0.279 g, 1.0 mmol), absolute ethanol (4 mL), and pyrrolidine (0.246 mL, 3.0 mmol). The mixture was stirred at reflux under nitrogen for 23 h. After this time, the reaction solvent was removed under reduced pressure and the residue was purified by silica gel chromatography. Compound **2a** was recovered as a white solid in 92% yield (0.305 g) ($R_f$ = 0.19 in hexanes/EtOAc 60:40 v/v): mp 122−124 °C; IR (KBr) 3403, 3052, 2971, 2938, 2907, 2839, 1768, 1692, 1575, 1438, 1349, 1258, 1119, 980, 927, 861, 747, 722, 637 cm-1; $^1$H NMR (500 MHz, $CDCl_3$) 7.37 (d, $J$ = 1.7 Hz, 1H), 6.99 (d, $J$ = 0.9 Hz, 1H), 4.37 (ddd, $J$ = 5.2, 2.8, 0.8 Hz, 1H), 4.23 (br s, 1H), 4.09 (d, $J$ = 16.2 Hz, 1H), 3.78 (d, $J$ = 16.2 Hz, 1H), 2.82−2.75 (comp, 2H), 2.20−2.11 (m, 1H), 2.04−1.87 (comp, 2H), 1.73 (dddd, $J$ = 12.6, 9.9, 4.2, 2.8 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 139.6, 132.5, 129.2, 121.7, 109.0, 108.3, 71.3, 49.9, 49.6, 32.7, 21.7; $m/z$ (ESI-MS) 333.0 [M + H]$^+$.

**Aminal 2b.** A 10 mL round-bottom flask was charged with 2-aminobenzaldehyde (0.121 g, 1.0 mmol), absolute ethanol (4 mL), and pyrrolidine (0.246 mL, 3.0 mmol). The mixture was stirred at reflux under nitrogen for 72 h. After this time, the reaction solvent was removed under reduced pressure and the residue was purified by silica gel chromatography. Compound **2b** was recovered as a white solid in 73% yield (0.127 g) ($R_f$ = 0.25 in EtOAc/MeOH 95:5 v/v): mp 63−64 °C; IR (KBr) 3246, 2966, 2826, 1608, 1585, 1478, 1383, 1255, 749 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 7.02 (app t, $J$ = 7.6 Hz, 1H), 6.95 (app d, $J$ = 7.4 Hz, 1H), 6.70 (app dt, $J$ = 7.4, 0.9 Hz, 1H), 6.54 (app d, $J$ = 7.9 Hz, 1H), 4.17−4.13 (m, 1H), 4.04 (d, $J$ = 15.6 Hz, 1H), 3.90 (d, $J$ = 15.6 Hz, 1H), 3.67 (br s, 1H), 3.03 (app dt, $J$ = 8.8, 5.5 Hz, 1H), 2.68 (app dt, $J$ = 8.8, 5.5 Hz, 1H), 2.18−2.09 (m, 1H), 1.97−2.07 (m, 1H), 1.96−1.87 (m, 1H), 1.66 (app tdd, $J$ = 12.3, 10.2, 4.4 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 137.6, 133.3, 128.6, 126.0, 125.5, 125.2, 124.3, 120.0, 118.9, 115.2, 72.4, 51.9, 50.9, 31.9, 21.3; $m/z$ (ESI-MS) 175.1 [M + H]$^+$.

**Aminal 2c.** To a stirred solution of 2-amino-3,5-dibromobenzaldehyde (0.279 g, 1.0 mmol) in 2-propanol (4 mL) was added piperidine (0.297 mL, 3.0 mmol). The mixture was heated to 140 °C for 48 h in a sealed tube. After this time, the reaction solvent was removed under reduced pressure and the residue was purified by silica gel chromatography. Compound **2c** was recovered as a white solid in 67% yield (0.232 g) ($R_f$ = 0.28 in Hex/EtOAc 70:30 v/v): mp 89−92 °C; IR (KBr) 3405, 2936, 2853, 2771, 1596, 1561, 1486, 1442, 1370, 1351, 1294, 1272, 1190, 1119, 856, 713 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 7.36 (d, $J$ = 2.1 Hz, 1H), 6.96 (d, $J$ = 1.4 Hz, 1H), 4.22 (s, 1H), 3.79 (br s, 1H), 3.72−3.59 (comp, 2H), 2.96−2.88 (m, 1H), 2.25−2.15 (m, 1H), 1.95−1.87 (m, 1H), 1.76 (app tt, $J$ = 10.1, 4.9 Hz, 1H), 1.71−1.64 (comp, 2H), 1.63−1.54 (m, 1H), 1.50−1.41 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 139.1, 132.5, 128.7, 122.3, 108.5, 108.3, 70.2, 56.0, 51.5, 31.9, 25.6. 21.3; $m/z$ (ESI-MS) 347.0 [M + H]$^+$.

**Aminal 2d.** To a stirred solution of 2-amino-3,5-dibromobenzaldehyde (0.279 g, 1.0 mmol) in isopropanol (4 mL) was added morpholine (0.260 mL, 3.0 mmol). The mixture was heated to 140 °C for 48 h in a sealed tube. After this time, the reaction solvent was removed under reduced pressure and the residue was purified by silica gel chromatography. Compound **2d** was recovered as a light brown solid in 15% yield (0.052 g) ($R_f$ = 0.15 in hexanes/EtOAc 80:20 v/v): mp 156−157 °C; IR (KBr) 3344, 2982, 2937, 2901, 2855, 1590, 1492, 1464, 1342, 1315, 1280, 1140, 1121, 1079, 1041, 861, 756, 730 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 7.42 (s, 1H), 7.00 (s, 1H), 4.25 (s, 1H), 4.05 (br s, 1H), 3.97 (app d, $J$ = 15.2 Hz, 1H), 3.91−3.77 (comp, 3H), 3.72−3.61 (comp, 2H), 2.91−2.84 (m, 1H), 2.42−2.36 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 138.5, 132.5, 128.8, 121.4, 109.3, 108.9, 69.2, 67.0, 66.9, 54.7, 48.3; $m/z$ (ESI-MS) 349.0 [M + H]$^+$.

**Aminal 2e.** To a 10 mL round-bottom flask with magnetic stir bar were added 2-amino-3,5-dibromobenzaldehyde (0.279 g, 1.0 mmol), absolute ethanol (4 mL), and 1,2,3,4-tetrahydroisoquinoline (0.381 mL, 3.0 mmol). The mixture was stirred at reflux under nitrogen for 16 h. After this time the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography. Compound **2e** was recovered as a white solid in 96% yield (0.378 g) ($R_f$ = 0.43 in hexanes/EtOAc 80:20 v/v): mp 145−147 °C; IR (KBr) 3408, 3065, 2934, 2899, 2846, 1590, 1480, 1334, 1280, 1234, 1117, 1006, 991, 865, 772, 735, 721, 685 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 7.43 (d, $J$ = 1.7 Hz, 1H), 7.37−7.27 (comp, 3H), 7.22 (app d, $J$ = 7.4 Hz, 1H), 7.07 (s, 1H), 5.28 (d, $J$ = 2.3 Hz, 1H), 4.39 (d, $J$ = 16.2 Hz, 1H), 4.31 (s, 1H), 3.81 (d, $J$ = 16.2 Hz, 1H), 3.19−3.02 (comp, 2H), 2.97−2.86 (m, 1H), 2.77−2.66 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 138.7, 134.7, 134.5, 132.4, 129.2, 128.8, 128.3, 126.5, 126.4, 121.7, 109.0, 108.7, 69.1, 55.3, 44.5, 29.1; $m/z$ (ESI-MS) 395.0 [M + H]$^+$.

**Aminal 2g.** To a 10 mL round-bottom flask with a magnetic stir bar were added 2-aminobenzaldehyde (0.121 g, 1.0 mmol), absolute ethanol (4 mL), and 1,2,3,4-tetrahydroisoquinoline (0.381 mL, 3.0 mmol). The mixture was stirred at reflux under nitrogen for 48 h. After this time the solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography. Compound **2g** was recovered as a yellow oil in 96% yield (0.227 g) ($R_f$ = 0.33 in hexanes/EtOAc 70:30 v/v): IR (KBr) 3387, 3024, 2916, 2837, 2791, 2740, 1725, 1606, 1583, 1487, 1424, 1339, 1305, 1249, 1112, 1044, 1021, 936, 749 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl3) 7.36 (dd, $J$ = 7.2, 1.7 Hz, 1H), 7.30−7.23 (comp, 2H), 7.20 (dd, $J$ = 7.2, 1.2 Hz, 1H), 7.07 (app t, $J$ = 7.6 Hz, 1H), 7.01 (app d, $J$ = 7.5 Hz, 1H), 6.77 (app dt, $J$ = 7.4, 1.1 Hz, 1H), 6.58 (app d, $J$ = 8.0 Hz, 1H), 5.16 (d, $J$ = 3.2 Hz, 1H), 4.35 (d, $J$ = 15.8 Hz, 1H), 3.87 (d, $J$ = 15.8 Hz, 1H), 3.86 (br s, 1H), 3.21 (ddd, $J$ = 11.4, 8.3, 4.8 Hz, 1H), 3.06 (ddd, $J$ = 14.0, 8.3, 5.7 Hz, 1H), 2.98 (app td, $J$ = 16.4, 4.8 Hz, 1H), 2.72 (app td, $J$ = 10.9, 5.3 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl3) $\delta$ 142.3, 135.8, 134.9, 129.3, 128.1, 127.5, 127.3, 126.5, 126.4, 119.8, 118.7, 115.6, 69.7, 56.0, 45.5, 29.4; $m/z$ (ESI-MS) 237.1 [M + H]$^+$.

**Aminal 2h.** A 10 mL microwave reaction tube was charged with a 10 × 8 mm SiC passive heating element, 2-aminobenzaldehyde (0.121 g, 1.0 mmol), $n$-BuOH (4 mL), and 1,2,3,4-tetrahydroisoquinoline (0.254 mL, 2.0 mmol). The reaction tube was sealed with a

Teflon-lined snap cap and heated in a microwave reactor at 250 °C (200 W, 80−120 psi) for 2 h. After cooling with compressed air flow, the reaction solvent was removed under reduced pressure and the residue was purified by silica gel chromatography. Compound **2h** was recovered as a yellow solid in 47% yield (0.111 g) in addition to **2g** (38% yield, 0.089 g). Characterization data for **2h** ($R_f$ = 0.14 in hexanes/EtOAc 80:20 v/v): mp 151−153 °C; IR (KBr) 3356, 3032, 2894, 2750, 1612, 1591, 1491, 1452, 1437, 1390, 1368, 1270, 1141, 1125, 1093, 1020, 746, 723 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 7.20−7.11 (comp, 3H), 7.07−7.00 (comp, 2H), 6.98 (app d, $J$ = 7.5 Hz, 1H), 6.73 (app dt, $J$ = 7.5, 1.1 Hz, 1H), 6.50 (dd, $J$ = 8.0, 0.9 Hz, 1H), 4.75−4.68 (m, 1H), 4.38 (d, $J$ = 16.1 Hz, 1H), 4.03 (d, $J$ = 15.1 Hz, 1H), 3.85 (d, $J$ = 16.1 Hz, 1H), 3.78−3.67 (comp, 2H), 3.33 (dd, $J$ = 16.8, 4.6 Hz, 1H), 2.81 (dd, $J$ = 16.8, 3.1 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 142.8, 134.0, 130.4, 128.8, 127.5, 127.2, 126.5, 126.3, 126.0, 118.7, 118.4, 114.8, 65.7, 54.9, 49.6, 34.8; $m/z$ (ESI-MS) 237.1 [M + H]$^+$.

**Aminal 2j.** A 10 mL microwave reaction tube was charged with a 10 × 8 mm SiC passive heating element, 2-aminobenzaldehyde (0.121 g, 1.0 mmol), $n$-BuOH (4 mL), and 2-methylpyrrolidine (0.306 mL, 3.0 mmol). The reaction tube was sealed with a Teflon-lined snap cap and heated in a microwave reactor at 250 °C (200 W, 100−150 psi) for 15 min. After cooling with compressed air flow, the reaction solvent was removed under reduced pressure and the residue was purified by silica gel chromatography. Compound **2j** was isolated as a yellow oil in 66% yield (0.124 g) ($R_f$ = 0.27 in EtOAc): IR (KBr) 3397, 2970, 1647, 1609, 1493, 1457, 1414, 1354, 1271, 1215, 1131, 1036, 747 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 7.01 (app t, $J$ = 7.8 Hz, 1H), 6.95 (app d, $J$ = 7.4 Hz, 1H), 6.64 (app t, $J$ = 7.4 Hz, 1H), 6.43 (app d, $J$ = 7.8 Hz, 1H), 4.23 (d, $J$ = 17.0 Hz, 1H), 3.75 (d, $J$ = 17.0 Hz, 1H), 3.59 (br s, 1H), 3.01 (app td, $J$ = 8.4, 4.4 Hz, 1H), 2.75 (app q, $J$ = 8.4 Hz, 1H), 1.98−1.75 (comp, 4H), 1.41 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 142.0, 127.4, 127.1, 117.0, 116.6, 114.0, 73.1, 50.8, 45.3, 39.8, 25.5, 19.8; $m/z$ (ESI-MS) 189.0 [M + H]$^+$.

In addition, compound **2k** was isolated as a yellow oil as a mixture of diastereomers in 26% yield (0.049 g), dr = 54:46 as determined by integration of one set of $^1$H NMR signals ($\delta_{major}$ 1.26 ppm, $\delta_{minor}$ 1.16 ppm) ($R_f$ = 0.45 in EtOAc): IR (KBr) 3386, 2961, 2870, 1608, 1494, 1375, 1302, 1262, 1154, 1041, 747 cm$^{-1}$; $^1$H NMR of major diastereomer (500 MHz, $CDCl_3$) 7.08−6.98 (comp, 2H), 6.77 (app dt, $J$ = 7.4, 1.1 Hz, 1H), 6.70−6.64 (comp, 1H), 4.07 (d, $J$ = 13.9 Hz, 1H), 3.99 (br s, 1H), 3.65−3.57 (m, 1H), 3.46 (d, $J$ = 13.9 Hz, 1H), 2.49−2.39 (m, 1H), 2.25−1.97 (comp, 2H), 1.74−1.48 (comp, 2H), 1.26 (d, $J$ = 6.1 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 143.1, 143.0, 127.4, 127.1, 127.0, 121.7, 119.2, 117.6, 117.2, 116.8, 113.6, 74.2, 70.8, 58.6, 53.3, 52.6, 45.7, 31.0, 30.7, 29.7, 28.8, 19.5, 18.6; $m/z$ (ESI-MS) 189.0 [M + H]$^+$.

**Synthesis of Aminoaldehyde 11.** To a 25 mL round-bottom flask with fitted with a magnetic stir bar were added 2-aminobenzyl alcohol (0.246 g, 2.00 mmol), methanol (6.25 mL), ($E$)-ethyl 7-oxohept-2-enoate[27a] (0.374 g, 2.20 mmol), and acetic acid (0.321 mL, 5.6 mmol). The resulting solution was cooled to 0 °C in an ice bath, and sodium cyanoborohydride (0.189 g, 3.00 mmol) was added. The solution was allowed to warm to room temperature and was stirred for 1 h, after which time the reaction was quenched with 5 mL of 5% aq $KHSO_4$ solution. The product was extracted with EtOAc (2 × 10 mL), and the extract was washed with satd $NaHCO_3$ (1 × 10 mL) followed by brine (1 × 10 mL). The organic layer was dried over sodium sulfate, filtered, and dried in vacuo. The crude product was purified by silica gel chromatography, and ethyl 7-((2-(hydroxymethyl)phenyl)amino)hept-2-enoate (**11′**) was obtained as a colorless oil in 91% yield (0.503 g) as a mixture of stereoisomers; ratio $E/Z$ = 3.55:1 ($R_f$ = 0.23 in hexanes/EtOAc 80:20 v/v). Characterization data of the $E$ isomer: IR (KBr) 3391, 2931, 1716, 1652, 1607, 1520, 1456, 1312, 1192, 1038, 927, 822, 748 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 7.21 (app td, $J$ = 7.8, 1.6 Hz, 1H), 7.04 (dd, $J$ = 7.8, 1.3 Hz, 1H), 6.96 (app dt, $J$ = 15.6, 6.9 Hz, 1H), 6.67−6.62 (comp, 2H), 5.83 (dt, $J$ = 15.6, 1.5 Hz, 1H), 4.63 (s, 2H), 4.17 (q, $J$ = 7.1 Hz, 2H), 3.15 (t, $J$ = 6.9 Hz, 2H), 2.25 (app qd, $J$ = 7.2, 1.4 Hz, 2H), 1.73−1.65 (comp, 2H), 1.64−1.57 (comp, 2H), 1.28 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 166.7, 148.7, 147.6, 129.5, 129.0, 124.2, 121.6, 116.2, 110.4, 64.7, 60.2, 43.1, 31.8, 28.8, 25.5, 14.2; $m/z$ (ESI-MS) 278.1 [M + H]$^+$.

A 10 mL round-bottom flask with a stir bar was charged with **11′** (0.277 g, 1 mmol, ratio of stereoisomers ($E/Z$) = 3.55:1), dichloromethane (3.57 mL), and manganese dioxide (0.522 g, 6.00 mmol), and the resulting solution was stirred at room temperature for 20 h. The reaction mixture was filtered through a pad of Celite and rinsed with dichloromethane (3 × 20 mL). The solvent was removed *in vacuo* and the residue was purified by silica gel chromatography, yielding both $E$ and $Z$ isomers. Pure $E$-isomer **11** was obtained as a bright yellow oil in 62% yield (0.198 g) ($R_f$ = 0.31 in hexanes/EtOAc 90:10 v/v): IR (KBr) 3331, 2984, 2745, 1647, 1521, 1457, 1265, 1040, 981, 870, 749 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 9.81 (s, 1H), 8.31 (br s, 1H), 7.46 (dd, $J$ = 7.9, 1.4 Hz, 1H), 7.42−7.35 (m, 1H), 6.95 (app dt, $J$ = 15.6, 6.9 Hz, 1H), 6.75−6.63 (comp, 2H), 5.87−5.81 (m, 1H), 4.18 (q, $J$ = 7.1 Hz, 2H), 3.33−3.19 (m, 2H), 2.36−2.21 (m, 2H), 1.81−1.68 (m, 2H), 1.67−1.56 (m, 2H), 1.28 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 193.9, 166.5, 150.7, 148.3, 136.7, 135.8, 121.8, 118.3, 114.7, 110.7, 60.2, 42.1, 31.8, 28.5, 25.5, 14.2; $m/z$ (ESI-MS) 276.3 [M + H]$^+$.

**Compound 12.** To a 5 mL round-bottom flask were added aldehyde **11** (0.25 mmol, 0.069 g), absolute ethanol (1 mL) and pyrrolidine (0.75 mmol, 0.062 mL). The resulting mixture was stirred at reflux for 48 h. The reaction mixture was cooled to room temperature and solvent was removed in vacuo. The residue was purified via silica gel chromatography (hexanes/EtOAc 80:20 v/v − EtOAc/MeOH/$NEt_3$ 74:25:1 v/v/v). Racemic compound **12** was obtained as a tan oil in 7% yield (0.0060 g) ($R_f$ = 0.44 in hexanes/EtOAc 80:20 v/v). Relative stereochemistry was determined using 2D NMR and $J$-coupling analysis: IR (KBr) 3329, 2933, 1717, 1654, 1577, 1522, 1458, 1338, 1160, 1041, 751 cm$^{-1}$; $^1$H NMR (500 MHz, $(CD_3)_2CO$) 7.08 (app td, $J$ = 7.3, 1.7 Hz, 1H), 6.94 (dd, $J$ = 7.3, 1.7 Hz, 1H), 6.78 (app d, $J$ = 8.2 Hz, 1H), 6.53 (app td, $J$ = 7.3, 3.3 Hz, 1H), 4.28−4.20 (m, 1H), 4.15−4.01 (comp, 3H), 3.47 (app td, $J$ = 10.7, 2.2 Hz, 1H), 2.87 (app t, $J$ = 12.8, 1H), 2.62−2.54 (dd, $J$ = 10.7, 4.7 Hz, 1H) 2.54−2.47 (m, 2H), 2.40−2.29 (m, 2H), 1.99−1.93 (m, 1H), 1.87−1.81 (m, 1H), 1.71−1.65 (m, 1H), 1.62−1.46 (comp, 6H), 1.25 (t, $J$ = 7.1 Hz, 3H), 1.09−0.99 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 172.2, 145.5, 130.1, 128.7, 115.3, 111.5, 109.7, 60.2, 59.5, 54.7, 51.8, 50.9, 48.0, 33.5, 25.4, 24.9, 23.4, 14.2; $m/z$ (ESI-MS) 327.5 [M−H]$^+$.

In addition, compound **13** was isolated as a yellow oil in 7% yield (0.0044 g) ($R_f$ = 0.47 in hexanes/EtOAc 90:10 v/v): IR (KBr) 3419, 2360, 2090, 1649, 1559, 1540, 1507, 1457 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 7.32 (s, 1H), 7.18−7.14 (m, 1H), 7.01 (dd, $J$ = 7.4, 1.2 Hz, 1H), 6.65−6.57 (comp, 2H), 4.45 (dd, $J$ = 10.8, 1.9 Hz, 1H), 4.30−4.19 (m, 2H), 3.94 (app d, $J$ = 13.6 Hz, 1H), 3.07−2.97 (m, 1H), 1.85−1.79 (m, 1H), 1.78−1.65 (comp, 3H), 1.54−1.44 (comp, 2H), 1.33 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 165.6, 145.5, 134.9, 132.1, 130.1, 124.5, 120.6, 116.7, 111.2, 60.4, 58.2, 46.7, 28.9, 25.0, 22.1, 14.3; $m/z$ (ESI-MS) 256.3 [M−H]$^+$.

In addition, compound **14** was isolated as a tan oil in 42% yield (0.0370 g) ($R_f$ = 0.20 in hexanes/EtOAc 70:30 v/v): IR (KBr) 3447, 2936, 2870, 2115, 1732, 1652, 1578, 1521, 1459, 1200, 1160, 1039, 751 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 9.80 (s, 1H), 8.29 (br s, 1H), 7.46−7.41 (m, 1H), 7.39−7.33 (m, 1H), 6.69−6.62 (comp, 2H), 4.12 (q, $J$ = 7.1 Hz, 2H), 3.29−3.15 (comp, 2H), 3.02−2.93 (m, 1H), 2.64−2.48 (comp, 5H), 2.32 (ddd, $J$ = 14.7, 7.3, 2.3 Hz, 1H), 1.80−1.63 (comp, 6H), 1.63−1.44 (comp, 4H), 1.24 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 193.8, 172.9, 150.8, 136.7, 135.7, 118.2, 114.5, 110.7, 60.3, 58.6, 49.5, 42.4, 36.4, 32.6, 29.2, 23.5, 23.2, 14.2; $m/z$ (ESI-MS) 347.2 [M + H]$^+$.

In addition, compound **15** was isolated as a tan oil in 22% yield (0.0228 g) ($R_f$ = 0.09 in $i$-$PrNH_2$/MeOH/EtOAc 1:25:74 v/v/v): IR (KBr) 3421, 2931, 1733, 1654, 1497, 1458, 1374, 1033 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 7.08 (app t, $J$ = 7.8 Hz, 1H), 6.91 (app d, $J$ = 7.3 Hz, 1H), 6.66−6.59 (comp, 2H), 4.13 (q, $J$ = 7.1 Hz, 2H), 3.89 (app t, $J$ = 5.7 Hz, 1H), 3.85 (d, $J$ = 14.6 Hz, 1H), 3.79 (d, $J$ = 14.6 Hz, 1H), 3.34−3.26 (m, 1H), 3.14−3.01 (comp, 2H), 2.99−2.92 (m, 1H), 2.61−2.51 (comp, 5H), 2.34 (dd, $J$ = 14.8, 7.3 Hz, 1H), 2.14−2.06 (m, 1H), 1.99−1.80 (comp, 4H), 1.78−1.72 (comp, 4H), 1.66−1.48

(comp, 4H), 1.43−1.33 (comp, 2H), 1.25 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.0, 144.7, 144.6, 127.4, 126.9, 121.0, 120.9, 116.6, 112.0, 60.3, 58.8, 52.3, 51.6, 49.6, 47.6, 47.5, 36.5, 36.4, 32.7, 30.6, 27.4, 27.3, 23.5, 23.4, 20.6, 14.2; $m/z$ (ESI-MS) 400.2 [M + H]$^+$.

**Aminoaldehyde 18.** To a 5 mL round-bottom flask were added aldehyde **11** (0.25 mmol, 0.069 g), absolute ethanol (1 mL), and piperidine (0.75 mmol, 0.074 mL). The resulting mixture was stirred at reflux for 96 h. The reaction mixture was cooled to room temperature, and solvent was removed in vacuo. The residue was purified via silica gel chromatography (hexanes/EtOAc 80:20 v/v−EtOAc/MeOH/$NEt_3$ 74:25:1 v/v/v). Compound **18** was obtained as an orange oil in 47% yield (0.0421 g) ($R_f$ = 0.32 in hexanes/EtOAc 50:50 v/v): IR (KBr) 3328, 2933, 2854, 2740, 1731, 1651, 1610, 1580, 1520, 1462, 1335, 1234, 1159, 1113, 1038, 877, 750, 663 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 9.79 (s, 1H), 8.30 (br s, 1H), 7.44 (app d, $J$ = 7.8 Hz, 1H), 7.36 (app t, $J$ = 7.8 Hz, 1H), 6.75−6.70 (comp, 2H), 4.11 (q, $J$ = 7.1 Hz, 2H), 3.21 (dd, $J$ = 12.7, 6.6 Hz, 2H), 3.02−2.91 (m, 1H), 2.52 (dd, $J$ = 14.2, 6.8 Hz, 1H), 2.49−2.43 (comp, 2H), 2.42−2.35 (comp, 2H), 2.15 (dd, $J$ = 14.2, 6.8 Hz, 1H), 1.74−1.63 (comp, 2H), 1.61−1.28 (comp, 10H), 1.24 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 193.7, 173.3, 150.8, 136.6, 135.7, 118.2, 114.5, 110.7, 61.6, 60.1, 49.4, 42.4, 35.1, 30.7, 28.9, 26.5, 24.9, 24.2, 14.2; $m/z$ (ESI-MS) 361.2 [M + H]$^+$.

***N,O*-Acetal 20.** A 10 mL microwave reaction tube was charged with a 10 × 8 mm SiC passive heating element, 2-amino-3,5-dibromobenzaldehyde (0.279 g, 1.0 mmol), PhMe (1 mL), and pyrrolidine (0.041 mL, 0.5 mmol). The reaction tube was sealed with a Teflon-lined snap cap and heated in a microwave reactor at 150 °C (200 W, 30−60 psi) for 30 min. After cooling with compressed air flow, the reaction mixture was loaded directly onto a column and purified by silica gel chromatography. Racemic compound **20** was obtained as a tan solid in 27% yield (0.0809 g) in addition to **2a** (58% yield, 0.0957 g). Characterization data for **20** ($R_f$ = 0.53 in hexanes/EtOAc 60:40 v/v). Relative stereochemistry was determined using 2D NMR and $J$-coupling analysis: mp 153−156 °C; IR (KBr) 3438, 3393, 3344, 2961, 1607, 1577, 1570, 1507, 1484, 1458, 1379, 1340, 1286, 1264, 1195, 1170, 1050, 865, 739 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 7.59 (d, $J$ = 2.2 Hz, 1H), 7.39 (d, $J$ = 2.1 Hz, 1H), 6.71 (d, $J$ = 2.2 Hz, 1H), 5.88 (d, $J$ = 2.1 Hz, 1H), 5.01 (br s, 2H), 4.76 (app d, $J$ = 4.6 Hz, 1H), 4.39 (d, $J$ = 9.8 Hz, 1H), 4.34 (br s, 1H), 4.15 (d, $J$ = 9.8 Hz, 1H), 3.11 (app td, $J$ = 8.8, 3.2 Hz, 1H), 2.69 (app q, $J$ = 8.8 Hz, 1H), 2.28−2.17 (m, 1H), 2.08−1.94 (comp, 2H), 1.93−1.84 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 142.6, 137.9, 134.2, 133.2, 132.9, 132.2, 124.5, 117.8, 111.5, 108.5, 108.2, 107.2, 77.3, 64.2, 58.3, 50.0, 33.1, 20.8; $m/z$ (ESI-MS) 611.8 [M + H]$^+$.

**Aminal 2a (Partially Deuterated According to eq 6).** To a 10 mL round-bottom flask fitted with a magnetic stir bar were added 2-amino-3,5-dibromobenzaldehyde (0.279 g, 1.0 mmol), EtOD (4 mL), and pyrrolidine (0.246 mL, 3.0 mmol). The resulting mixture was stirred at reflux for 24 h. After this time, the solvent was removed under reduced pressure and the product was dissolved in EtOAc (10 mL). This solution was washed with distilled water (3 × 10 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The resultant residue was purified by silica gel chromatography. Compound **2a** was recovered as a white solid in 77% yield (0.257 g) ($R_f$ = 0.33 in hexanes/EtOAc 60:40 v/v): IR (KBr) 3404, 3053, 2971, 2937, 2903, 2839, 1591, 1482, 1333, 1277, 1239, 1222, 1132, 880, 724 cm$^{-1}$; 1H NMR (500 MHz, $CDCl_3$) 7.39 (d, $J$ = 2.1 Hz, 1H), 7.02−6.99 (m, 1H), 4.47−4.36 (m, 1H), 4.24 (br s, 1H), 4.15−4.06 (comp, 1H, 50% D), 3.84−3.75 (comp, 1H, 54% D), 2.91−2.73 (comp, 2H), 2.24−2.11 (m, 1H), 2.08−1.88 (comp, 2H), 1.81−1.68 (m, 1H); $m/z$ (ESI-MS) 334.1 [M + H]$^+$.

**Aminal 2e (Partially Deuterated According to eq 7).** To a 10 mL round-bottom flask fitted with a magnetic stir bar were added 2-amino-3,5-dibromobenzaldehyde (0.279 g, 1.0 mmol), EtOD (4 mL), and 1,2,3,4-tetrahydroisoquinoline (0.381 mL, 3.0 mmol). The resulting mixture was stirred at reflux for 16 h. After this time, the solvent was removed under reduced pressure and the product was dissolved in $CH_2Cl_2$ (10 mL). This solution was washed with distilled water (3 × 10 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The resultant residue was purified by silica gel chromatography. Compound **2e** was recovered as a white solid in 95% yield (0.375 g) ($R_f$ = 0.43 in hexanes/EtOAc 80:20 v/v): IR (KBr) 3408, 3066, 2955, 2911, 2847, 1509, 1480, 1365, 1316, 1281, 1163, 1117, 991, 865, 735, 721 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 7.44 (d, $J$ = 2.0 Hz, 1H), 7.37−7.25 (comp, 3H), 7.22 (app d, $J$ = 7.4 Hz, 1H), 7.07 (d, $J$ = 1.5 Hz, 1H), 5.32−5.23 (comp, 1H, 33% D), 4.43−4.34 (comp, 1H, 33% D), 4.34−4.28 (comp, 1H), 3.84−3.73 (comp, 1H, 37% D), 3.17−3.02 (comp, 2H), 2.97−2.86 (m, 1H), 2.74−2.64 (m, 1H); $m/z$ (ESI-MS) 395.3 [M + H]$^+$.

**Aminal 2e (Partially Deuterated According to eq 8).** *N,N*-Dideutero-2-amino-3,5-dibromobenzaldehyde was produced by dissolving 2-amino-3,5-dibromobenzaldehyde (0.279 g, 1.0 mmol) in EtOD (1 mL), heating to reflux, allowing to cool to room temperature, removing solvent in vacuo, and repeating this process two more times. 1-Hydro-2-deutero-3,4-dihydroisoquinoline was produced from 1,2,3,4-tetrahydroisoquinoline (0.381 mL, 3.0 mmol) using the same process. To a 10 mL round-bottom flask fitted with a magnetic stir bar were added *N,N*-dideutero-2-amino-3,5-dibromobenzaldehyde (0.281 g, 1.0 mmol), EtOD (4 mL), and 1-hydro-2-deutero-3,4-dihydroisoquinoline (0.403 g, 3.0 mmol). The resulting mixture was stirred at reflux for 24 h. After this time, the solvent was removed under reduced pressure and the product was dissolved in $CH_2Cl_2$ (10 mL). This solution was washed with distilled water (3 × 10 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The resultant residue was purified by silica gel chromatography. Compound **2e** was isolated as a white solid in 87% yield (0.344 g) ($R_f$ = 0.43 in hexanes/EtOAc 80:20 v/v): IR (KBr) 3413, 3065, 3023, 2932, 2913, 2868, 2154, 1590, 1475, 1356, 1281, 1013, 1001, 863, 730, 721, 703, 685, 550 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 7.44 (d, $J$ = 2.0 Hz, 1H), 7.37−7.25 (comp, 3H), 7.22 (app d, $J$ = 7.4 Hz, 1H), 7.07 (d, $J$ = 1.5 Hz, 1H), 5.32−5.23 (comp, 1H, 30% D), 4.43−4.34 (comp, 1H, 40% D), 4.34−4.28 (comp, 1H), 3.84−3.73 (comp, 1H, 44% D), 3.17−3.02 (comp, 2H), 2.97−2.86 (m, 1H), 2.74−2.64 (m, 1H); $m/z$ (ESI-MS) 397.3 [M + H]$^+$.

In addition, partially deuterated THIQ was isolated as a colorless liquid in 98% yield (0.392 g) ($R_f$ = 0.13 in $i$-$PrNH_2$/MeOH/EtOAc 2:10:78 v/v/v): IR (KBr) 3316, 2922, 2360, 1496, 1454, 1261, 1120, 745 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 7.17−7.04 (comp, 3H), 7.00 (app t, $J$ = 4.2 Hz, 1H), 4.04−3.95 (comp, 1H, 12.5% D), 3.14 (t, $J$ = 5.8 Hz, 2H), 2.80 (t, $J$ = 5.8 Hz, 2H), 1.70 (s, 1H); $m/z$ (ESI-MS) 134.3 [M + H]$^+$.

**Aminal 2a (Partially Deuterated According to eq 9).** To a 10 mL round-bottom flask fitted with a magnetic stir bar were added 2-amino-3,5-dibromobenzaldehyde (0.279 g, 1.0 mmol), absolute ethanol (2 mL), EtOD (2 mL), and pyrrolidine (0.246 mL, 3.0 mmol). The resulting mixture was stirred at reflux for 24 h. After this time, the solvent was removed under reduced pressure, and the product was dissolved in EtOAc (10 mL). This solution was washed with distilled water (3 × 10 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The resultant residue was purified by silica gel chromatography. **2a** was recovered as a white solid in 85% yield (0.283 g) ($R_f$ = 0.33 in hexanes/EtOAc 60:40 v/v): IR (KBr) 3403, 3054, 2937, 2906, 2839, 1592, 1485, 1347, 1291, 1222, 1148, 1119, 979, 881, 861, 747, 725 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 7.37 (dd, $J$ = 2.1, 0.6 Hz, 1H), 6.98 (d, $J$ = 0.9 Hz, 1H), 4.37 (ddd, $J$ = 5.0, 2.6, 0.8 Hz, 1H), 4.23 (br s, 1H), 4.12−4.03 (comp, 1H, 14% D), 3.81−3.74 (comp, 1H, 18% D), 2.89−2.71 (comp, 2H), 2.27−2.09 (m, 1H), 2.09−1.84 (comp, 2H), 1.73 (dddd, $J$ = 12.6, 9.8, 4.2, 2.6 Hz, 1H); $m/z$ (ESI-MS) 333.0 [M + H]$^+$.

**Aminal 2e (Partially Deuterated According to eq 10).** To a 10 mL round-bottom flask fitted with a magnetic stir bar were added 2-amino-3,5-dibromobenzaldehyde (0.279 g, 1.0 mmol), absolute ethanol (2 mL), EtOD (2 mL), and 1,2,3,4-tetrahydroisoquinoline (0.381 mL, 3.0 mmol). The resulting mixture was stirred at reflux for 16 h. After this time, the solvent was removed under reduced pressure and the product was dissolved in $CH_2Cl_2$ (10 mL). This solution was washed with distilled water (3 × 10 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The resultant residue was purified by silica gel chromatography. Compound **2e** was recovered as a white solid in 95% yield (0.377 g) ($R_f$ = 0.43 in hexanes/EtOAc 80:20 v/v): IR (KBr) 3411, 2932, 2345, 1735, 1718, 1654, 1648, 1590, 1480, 1458, 1281, 1162, 1120, 736 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 7.43 (d, $J$ =


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1.7 Hz, 1H), 7.37–7.27 (comp, 3H), 7.22 (app d, $J$ = 7.4 Hz, 1H), 7.07 (s, 1H), 5.29–5.26 (comp, 1H, 13% D), 4.42–4.35 (comp, 1H, 6% D), 4.34–4.28 (comp, 1H), 3.84–3.76 (comp, 1H, 10% D), 3.13–3.02 (comp, 2H), 2.97–2.86 (m, 1H), 2.74–2.64 (m, 1H); $m/z$ (ESI-MS) 395.0 $[M + H]^+$.

**Aminal 2a (Partially Deuterated According to eq 11).** To a 10 mL round-bottom flask fitted with a magnetic stir bar were added 2-amino-3,5-dibromobenzaldehyde (0.279 g, 1.0 mmol), absolute ethanol (4 mL), and 2,2-dideuteropyrrolidine[27b] (0.219 g, 3.0 mmol). The resulting mixture was stirred at reflux for 3.5 days. After this time, the solvent was removed under reduced pressure and the product was dissolved in EtOAc (10 mL). This solution was washed with distilled water (3 × 10 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The resultant residue was purified by silica gel chromatography. Compound **2a** was recovered as a white solid in 77% yield (0.258 g) ($R_f$ = 0.33 in hexanes/EtOAc 60:40 v/v): IR (KBr) 3404, 3055, 2937, 2902, 2839, 2083, 1592, 1483, 1438, 1348, 1266, 1159, 1123, 963, 866, 741 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 7.39 (dd, $J$ = 2.1, 0.6 Hz, 1H), 7.00 (d, $J$ = 0.9 Hz, 1H), 4.48–4.36 (comp, 1H, 22% D), 4.24 (br s, 1H), 4.12 (d, $J$ = 16.3 Hz, 1H), 3.79 (d, $J$ = 16.3 Hz, 1H), 2.83–2.77 (comp, 2H, 78% D), 2.21–2.12 (m, 1H), 2.06–1.87 (comp, 2H), 1.74 (dddd, $J$ = 12.6, 9.8, 4.2, 2.7 Hz, 1H); $m/z$ (ESI-MS) 335.1 $[M + H]^+$.

**Aminal 2e (Partially Deuterated According to eq 12).** To a 10 mL round-bottom flask fitted with a magnetic stir bar were added 2-amino-3,5-dibromobenzaldehyde (0.279 g, 1.0 mmol), absolute ethanol (4 mL), and 1-deutero-1,2,3,4-tetrahydroisoquinoline[27c] (0.403 g, 3.0 mmol). The resulting mixture was stirred at reflux for 16 h. After this time, the solvent was removed under reduced pressure and the product was dissolved in $CH_2Cl_2$ (10 mL). This solution was washed with distilled water (3 × 10 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The resultant residue was purified by silica gel chromatography. Compound **2e** was recovered as a white solid in 96% yield (0.381 g) ($R_f$ = 0.43 in hexanes/EtOAc 80:20 v/v): IR (KBr) 3408, 3066, 2954, 2911, 2846, 2154, 1590, 1474, 1281, 1138, 1117, 1012, 997, 862, 769, 729, 683 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 7.42 (d, $J$ = 2.1 Hz, 1H), 7.35–7.25 (comp, 3H), 7.21 (app d, $J$ = 7.4 Hz, 1H), 7.06 (d, $J$ = 0.8 Hz, 1H), 5.29–5.25 (comp, 1H, 65% D), 4.42–4.34 (comp, 1H), 4.34–4.26 (comp, 1H), 3.79 (d, $J$ = 16.3 Hz, 1H), 3.18–3.02 (comp, 2H), 2.98–2.85 (m, 1H), 2.76–2.64 (m, 1H); $m/z$ (ESI-MS) 395.0 $[M + H]^+$.

**Aminal 2e (Partially Deuterated According to eq 13).** To a 10 mL round-bottom flask fitted with a magnetic stir bar were added 2-amino-3,5-dibromobenzaldehyde (0.279 g, 1.0 mmol), absolute ethanol (4 mL), 1,2,3,4-tetrahydroisoquinoline (0.190 mL, 1.5 mmol), and 1,1-dideutero-3,4-dihydro-2*H*-isoquinoline[27d] (0.203 g, 1.5 mmol). The resulting mixture was stirred at reflux for 16 h. After this time, the solvent was removed under reduced pressure and the product was dissolved in $CH_2Cl_2$ (10 mL). This solution was washed with distilled water (3 × 10 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The resultant residue was purified by silica gel chromatography. Compound **2e** was recovered as a white solid in 96% yield (0.378 g) ($R_f$ = 0.43 in hexanes/EtOAc 80:20 v/v): IR (KBr) 3412, 3064, 2932, 2905, 2867, 1590, 1478, 1338, 1280, 1162, 1121, 1030, 1004, 861, 770, 736, 722, 686 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 7.44 (d, $J$ = 2.1 Hz, 1H), 7.37–7.26 (comp, 3H), 7.22 (app d, $J$ = 7.5 Hz, 1H), 7.07 (d, $J$ = 1.0 Hz, 1H), 5.30–5.24 (comp, 1H, 34% D), 4.42–4.35 (comp, 1H), 4.34–4.29 (comp, 1H), 3.80 (d, $J$ = 16.2 Hz, 1H), 3.17–3.03 (comp, 2H), 2.98–2.85 (m, 1H), 2.76–2.65 (m, 1H); $m/z$ (ESI-MS) 395.9 $[M + H]^+$.

## ASSOCIATED CONTENT

### Supporting Information

NMR spectra for all reported compounds. Cartesian coordinates, energies, and thermodynamic corrections for all reported structures. This information is available free of charge via the Internet at http://pubs.acs.org.

## AUTHOR INFORMATION

### Corresponding Author

*E-mail: houk@chem.ucla.edu, seidel@rutchem.rutgers.edu.

### Notes

The authors declare no competing financial interest.

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